

10/581321

P20 Rec'd PCT/PTO 02 JUN 2006

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MIT/PCT-197

Re: International Patent Application N° PCT/ES2004/000549

Ladies & gentlemen,

We reply hereto in due time to the WO issued under Rule 66 PCT on 01.03.06 by submitting a new set of amended claims under Art. 34 PCT wherein all the objections raised in that WO have been duly considered.

Support for the amendments introduced

* Independent claim 1 has been amended as follows:

In view of comment on item VIII.7- of the WO, the term "blocking agent of the electrical activity of the damaged nerve ending of the neuroma" has been replaced by a term, taken from the description as formerly filed, which tries to better define the technical feature involved. The replacement term now reads (in cursive what has been added): "blocking agent of the electrical activity of the damaged nerve ending of the neuroma, *as consequence of its blocking action on the ion channels,...*". That more accurate definition of the technical feature is fully explained in page 4, lines 17-33 of the specification as formerly filed, therefore not involving the addition of fresh technical matter into the international application (IA).

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Moreover, as far as in comments on item V.3-, the examiner objected the novelty of claim 1 and depending claims thereon, in view of D1, we have disclaimed the neurotrophic factor stimulators disclosed therein (see D1, page 5, lines 3-6) even though, the action of those stimulators, is not disclosed in D1 as being exerted on voltage-dependent channels, in spite of the statement made by the examiner and that we presume is based on his/her own knowledge.

* Claim 5 has been amended as follows:

The term "n-benzyl analogues of compounds such as tocainide, mexiletine,....", which was not objected in the WO, has been replaced by "n-benzyl analogues of tocainide, mexiletine,". The formerly file term leaves the reader in doubt about as which meaning refers to. Whether mexiletine and the remaining compounds are all claimed as n-benzyl analogues. Only n-benzyl analogues of tocainide are claimed, together with tocainide as such, mexiletine, lidocaine, etc....

* Claim 12 has been amended as follows:

The same redefinition of the term "blocking agent", as used in amended claim 1, has been introduced herein.

The same disclaimer as used in amended claim 1, has been also introduced herein, with the addition of lidocaine, that is also disclaimed in view of the examiner comments on item V.3- of the WO.

* Claim 19 has been amended as follows:

The same redefinition of the term "blocking agent", as used in amended claims 1 and 12, has been introduced herein.

The same disclaimer as used in amended claim 1 has been also introduced herein.

Novelty

We notice the novelty and inventive step recognition made in the WO with regards to formerly filed claims 5-11 and 18-25 (Comments on item V.5-).

Independent claims 1, 12 and 19, as now amended, in our view, fulfill novelty requirement after a more precise definition of the term "blocking agent" and the disclaimer/s introduced, motivated by the accidental disclosures found in the state of the art. As a way of example, the accidental character of D3 and D4 for claims 12-14 is evident in view of the different use the ophthalmic lidocaine compositions are applied to, in those prior art documents.

Inventive step

We do not agree with the statement made by the examiner in the comments on item V.4- with regards to claims 4 and 18. Those claims, depending respectively on claims 1-3 and on claims 15-17, cover several families of compounds, known by a different physiological action than the technical feature now claimed in the IA. For each family claimed, at least one specific compound is given. Thus:

- a) Antiepileptics: phenytoin and lamotrigine
- b) Anticonvulsants: gabapentin
- c) Anti-arrhythmics: mexiletine
- d) Tricyclic antidepressants: amitriptyline
- e) Local anaesthetics: lidocaine and tocainide

All the families covered in claims 4 and 18 must exert their physiological action throughout blockage of ion channels because of their respective claim dependencies. Therefore, a strong presumption exists, supported by the specific compounds given in the specification for each family, that any other member of any of those families which acts by blocking ion channels, can also be used for the preparation of medicinal products for the treatment of eye surface dryness caused by photorefractive surgery.

Accordingly we believe that present set of amended claims also fulfills the inventive step requirement.

We respectfully request, in case the examiner would not share our opinion about novelty and inventive step accomplishment of all the claims as amended, to have an additional opportunity to submit further amendments according to Rule 66.4 PCT. Moreover, this representative would be willing to have any informal communication, according to Rule 66.6 PCT, in case the examiner in charge would consider it necessary in order to solve any remaining doubt or objection.

Very truly yours,

ELZABURU

Manuel Illescas

Enclosures :

New replacement pages 17-20 with amended claims 1-25

CLAIMS

1. Use of a blocking agent of the electrical activity of the damaged nerve endings of the neuroma, as a
5 consequence of its blocking action on the ion channels, excluding neurotrophic factor stimulators, particularly selected from: neotrofin, idebenone, CB-1093, (1-(1-butyl)-4-(2-oxo-1-benzimidazolone) piperidine, SS-701, KT-711, ONO-2506 and clenbuterol, for the preparation
10 of a medicinal product for the treatment of dryness of the surface of the human eye caused by photorefractive surgery.
2. Use according to claim 1, in which the photorefractive surgery is an excimer laser
15 photorefractive keratectomy or a laser-assisted in situ keratomileusis.
3. Use according to any one of the preceding claims, characterized in that the blocking agent is selected from those that exert their action on the voltage-
20 dependent sodium, calcium, chlorine and potassium channels.
4. Use according to any one of the preceding claims, characterized in that the blocking agent is selected from the group comprising antiepileptics,
25 anticonvulsants, anti-arrhythmic drugs, tricyclic antidepressants and local anaesthetics, and combinations thereof.
5. Use according to claim 4, characterized in that the blocking agent is selected from the group comprising
30 lidocaine, tocainide, n-benzyl analogues of tocainide, mexiletine, lamotrigine, carbamazepine, phenytoin, amitriptyline, N-phenylethyl amitriptyline, desipramine, gabapentin, nifekalant, venlafaxine, nefazodone, pregabalin, and the pharmaceutically
35 acceptable salts thereof.

6. Use according to claim 5, characterized in that the blocking agent is carbamazepine.

7. Use according to claim 5, characterized in that the blocking agent is phenytoin.

5 8. Use according to claim 5, characterized in that the blocking agent is mexiletine.

9. Use according to claim 5, characterized in that the blocking agent is lidocaine.

10 10. Use according to claim 5, characterized in that the blocking agent is tocaidine.

11. Use according to claim 5, characterized in that the blocking agent is pregabalin.

12. Pharmaceutical composition for ophthalmic application that comprises a therapeutically effective amount of a blocking agent of the electrical activity of the damaged nerve endings of the neuroma, as a consequence of its blocking action on the ion channels, excluding neurotrophic factor stimulators, particularly selected from: neotrofin, idebenone, CB-1093, (1-(1-butyl)-4-(2-oxo-1-benzimidazolone) piperidine, SS-701, KT-711, ONO-2506 and clenbuterol; and also excluding lidocaine, together with suitable amounts of pharmaceutically acceptable excipients for constituting an ophthalmic formulation.

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25 13. Composition according to claim 12, characterized in that the blocking agent is in an amount between 0.0005 and 1% (w/v).

14. Composition according to claim 13, characterized in that the blocking agent is in an amount between 0.0005 and 0.1% (w/v).

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15. Method of treatment of a mammal, including a human, suffering from dryness of the ocular surface caused by photorefractive surgery, which comprises the ophthalmic administration of an agent for blocking the electrical activity of the damaged nerve endings of the neuroma, as a consequence of its blocking action on the ion channels, excluding neurotrophic factor stimulators, particularly selected from: neotrofin, idebenone, CB-1093, (1-(1-butyl)-4-(2-oxo-1-benzimidazolone) piperidine, SS-701, KT-711, ONO-2506 and clenbuterol, together with suitable amounts of pharmaceutically acceptable excipients for constituting a topical formulation.

16. Method according to claim 15, characterized in that the photorefractive surgery is an excimer laser photorefractive keratectomy or a laser-assisted in situ keratomileusis.

17. Method according to any one of the claims 15-16, characterized in that the blocking agent is selected from those that exert their action on the voltage-dependent sodium, calcium, chlorine and potassium channels.

18. Method according to any one of the claims 15-17, characterized in that the blocking agent is selected from the group comprising antiepileptics, anticonvulsants, anti-arrhythmic drugs, tricyclic antidepressants and local anaesthetics, and combinations thereof.

19. Method according to claim 18, characterized in that the blocking agent is selected from the group comprising lidocaine, tocainide, n-benzyl analogues of tocainide, mexiletine, lamotrigine, carbamazepine, phenytoin, amitriptyline, N-phenylethyl amitriptyline, desipramine, gabapentin, nifekalant, venlafaxine,

nefazodone, pregabalin, and the pharmaceutically acceptable salts thereof.

20. Method according to claim 19, characterized in that the blocking agent is carbamazepine.

5 21. Method according to claim 19, characterized in that the blocking agent is phenytoin.

22. Method according to claim 19, characterized in that the blocking agent is mexiletine.

10 23. Method according to claim 19, characterized in that the blocking agent is lidocaine.

24. Method according to claim 19, characterized in that the blocking agent is tocaidine.

25. Method according to claim 19, characterized in that the blocking agent is pregabalin.

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